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Synthesis of 2, 4-disubstituted acridones and their evaluation for anticancer activity in MDR cells

N.B Lonikar[1], Y.C Mayur[2], S .M. Sonvane[3], D.Nagraju[2] and D.S.Gujrathi[1]

[1]Shivlingeshwar College of Pharmacy, Hasegaon, Latur
[2]V.L. College of Pharmacy, Raichur
[3]Dayanand College of Pharmacy, Latur

ABSTRACT

Synthesis of 2, 4-dimethylacridone starts with 2-[(2, 4-dimethylphenyl) amino] Benzoic acid, which was obtained by Ullmann condensation between 2-halogenbenzoic acid and 2, 4-dimethylamine. Ullman showed that traces of copper activate the halogen in 2-halobenzoic acid that it can be condensed with any aromatic amine. The 2, 4-dimethylphenylamino-benzoic acid was cyclized with polyphosphoric acid to get 2, 4-dimethylacridone. N-Alkylation is carried out by stirring 24 hours of acridone at room temperature with alkylating agent bromochloropropane or bromochlorobutane in a two phase system consisting of an organic solvent (Tetrahydrofuran) and 6 N aqueous potassium hydroxide solution in the presence of tetrabutylammonium bromide leads to the formation of respective 10-(3-chloropropyl) or 10-(4-chlorobutyl) acridone in good yield.

Key Word: - 2, 4 Dimethyl Acridone, Multi Drug Resistance Cells,

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INTODUCTION

The interaction of acridone derivatives with P-glycoprotein is not related to their DNA-interaction capabilities, but deserves to be mentioned as new and important strategy for chemotherapy[1].

Acquired or intrinsic resistance of cancer cells to anticancer drugs limits chemotherapy. Cross resistance phenomena are generally observed, as one drug leads to chemically and functionally unrelated drugs (Multidrug resistance)[2]. Several biochemical mechanisms may account for

MDR. One important mechanism involves a protein, called P-glycoprotein, which actively pumps the anticancer drugs out of the cells, thus reducing their activity[3]. There is a negative correlation between expression levels of P-glycoprotein and chemosensitivity or survival in a range of human malignancies. P-glycoprotein is an important drug target in the treatment of multidrug resistance cancer, as the inhibition of the protein might improve chemotherapy success rate. An important point to consider in the design of inhibitors in that they should be devoid of cytotoxicity and other pharmacological properties[4]. Several compounds have been tested as P-glycoprotein inhibitors and among them acridone derivatives a series of 4-carboxamide acridones have been prepared and tested and one molecule designed as GF-120918 displayed interesting properties[5].

A survey of chemical literature was revealed that the acridone ring nucleus substituted at N^{10} -position[6] with tertiary amino groups (Morpholino, Piperidino, N-Methylpiperazino, Diethylamino, Diethanolamino and [(B-Hydroxyethyl) piperazino] at a distance of 3 to 4 carbons from the hydrophobic acridone ring have been not reported. Several 9-acridone derivatives with or without an alkyl side chain, attached to N^{10} - position have been found to exhibit better anti-MDR and anticancer activities.

In view of the above facts, it is planned to,

1. Synthesize a series of N^{10} -substituted acridone derivatives with different secondary amine substitution.
2. Characterization by ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic methods.
3. Screening for anticancer activity and cytotoxicity in KBCh^{R}-8-5-cells or anti-MDR activity.

MATERIALS AND METHODS

Melting points were determined by using Toshniwal apparatus in open capillaries and are uncorrected. The purity of compounds was checked by TLC on silica gel G plates using chloroform: methanol (9:1) solvent system and UV lamp used as a visualizing agent. $_{1}$HNMR Spectra on a Varian EM-200, advance 300 MHZ spectrophotometer using DMSO solvent and MS as internal standard (chemical shift values expressed in δ ppm). $_{13}$C NMR spectra are also carried on same apparatus using same solvent. Mass spectra by EIMS technique on an Autospec. Mass spectrometer.

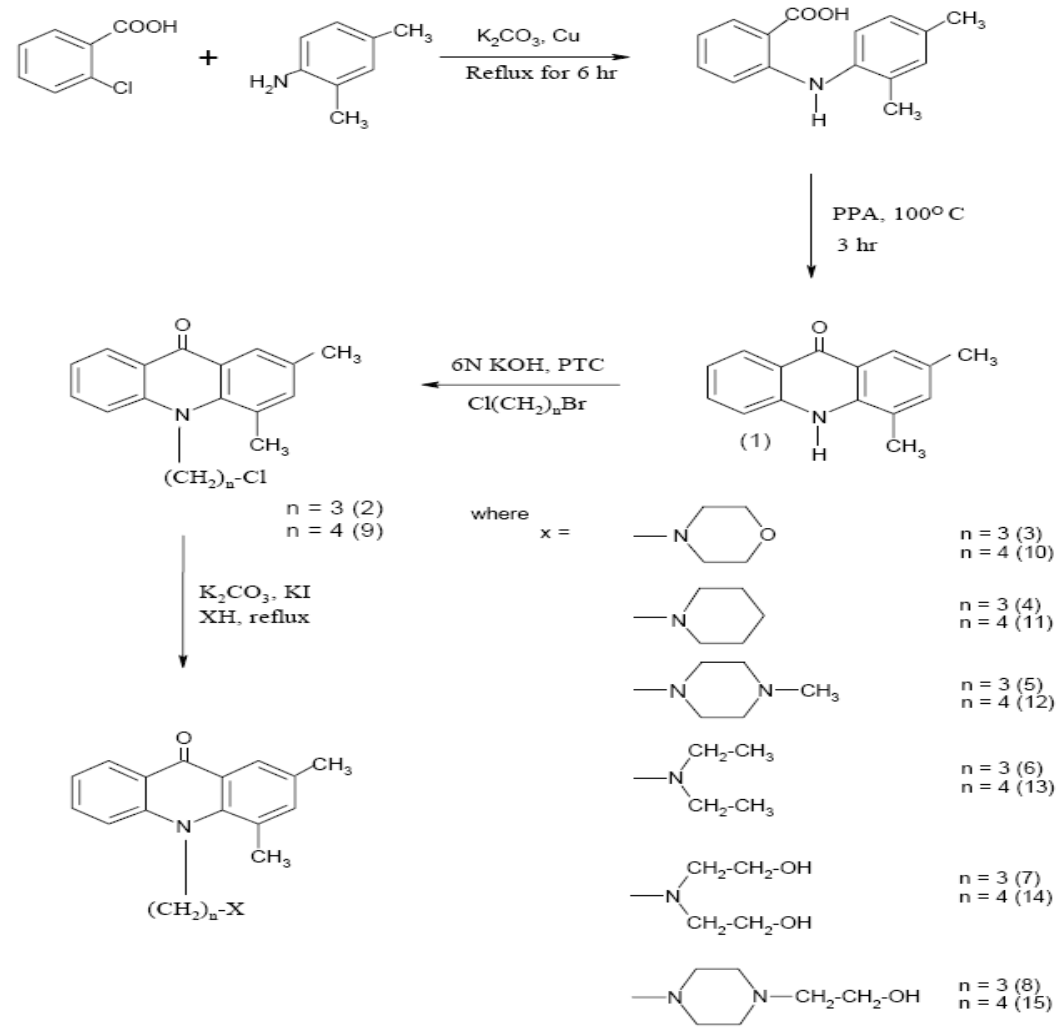
Synthesis of compound:

Preparation of 2-[(2, 4-dimethylphenyl) amino] benzoic acid :(C)

To a mixture of o- chlorobenzoic acid **(A)** (5g, 0.032 mmole), 2, 4-dimethyl aniline **(B)** (3.97ml) and copper powder (0.2 g) in 30ml isoamyl alcohol, dry potassium carbonate (4.41 g) was slowly added and the contents were allowed to reflux for 6 hours on an oil bath. The isoamyl alcohol as removed by steam distillation and the mixture poured into one litre of hot water and acidified with concentrated hydrochloric acid. Precipitate formed was filtered, washed with hot water and collected. The crude acid was dissolved in aqueous sodium hydroxide solution, boiled in the presence of activated charcoal and filtered. On acidification of the filtrate with concentrated hydrochloric acid, light brown precipitate was obtained which was washed with hot water and recrystallised from aqueous methanol to give light yellow solid yield 26.01%, mp 176^{o}C).

METHODOLOGY

SCHEME – 1



Cyclization of 2-[(2, 4-Dimethylphenyl) amino] benzoic acid to 2, 4-methylacridone(1)

Six grams of 2-[(2, 4-Dimethylphenyl) amino] benzoic acid **(C)** was taken in a round bottom flask to which was added 60 g of polyphosphoric acid. Shaken well and heated on a water bath at 100^{o}C for 3 hours. Appearance of yellow colour indicated the completion of the reaction. Then, it was poured into one litre of hot water and made alkaline by liquor ammonia. The light brown precipitate that formed was filtered, washed with hot water and collected. The sample of 2, 4-Dimethylacridone **(1)** was recrystallised from acetic acid (yield 68.11%, mp318^{o}C). Further, purity of the compound was checked by TLC (chloroform: methanol = 9:1). $C_{14}H_{13}NO$Anaiytical calculation: $_{1}$H- NMR: δ 7.2-8.2 (m, 6H,Ar-H), 2.35 (S, 3H,2CH_3), 2.55 (S, 3H, CH_3), 10.55 (S,1H,NH), $_{13}$C-NMR: δ 20.65 (C_2-CH_3), 17.74 (C_4-CH_3), 177.57 (C_9),141.125 (C_{10}', C_4'),

137.81 ($C_{8'}$, $C_{9'}$), 135.57(C_7), 132.66(C_5), 129.69 (C_6), 124.96 (C_3),120.90 (C_1), 120.77 (C_8), 120.53 (C_4), 117.98(C_2).LCMS (m/z): 224,222

10-(3-N-Chloropropyl)-2, 4-dimethylacridone (2)

One gram (0.0021mmole) of 2,4-dimethylacridone was dissolved in 20ml tetrahydrofuran and added 25 ml of 6 N potassium hydroxide and 0.74g tetrabutylammonium bromide to it. The reaction mixture was stirred at room temperature for half an hour and added 1-bromo-3-chloropropane slowly into the reaction mixture stirred for 24 hours at room temperature. Tetrahydrofuran was evaporated and the aqueous layer was extracted with chloroform. The chloroform layer was washed with water and organic layer dried over anhydrous sodium sulphate and rotaevaporated. The crude product was purified by column chromatography by using the solvent system of chloroform: methanol (9:1) to give yellow an solid of the product 10-(3-N-chloropropyl)- 2, 4-dimethylacridone **(2)** $C_{18}H_{18}NOCl$ yield 46%, mp 158^oC).

10-(3-N-Morpholinopropyl) - 2, 4-dimethylacridone (3)

One gram (0.0021mmole) of 10-(3-N-Chloropropyl)-2, 4-dimethylacridone was dissolved in 30ml of acetonitrile to which added 1.38g potassium iodide and 2.29g of potassium carbonate and refluxed for 30 minutes. Then 1.04ml of morpholine was added in that and refluxed for additional 20 hours. The contents were cooled, diluted with water and extracted with chloroform. The chloroform layer was washed with water thrice and dried over anhydrous sodium sulphate and evaporated to give an oily product. The oily product was purified by column chromatography. The light yellow oily product was dissolved in dry acetone and treated with ethereal hydrochloride. The Hydrochloride salt of the 10-(3-N-morpholinopropyl)-2, 4-dimethylacridone **(3)** was obtained (yield 58%, mp 159^oC). $C_{22}H_{26}N_2O_2$.HCl,analytical cal.:- ^{13}C-NMRδ 17.86 (C_4-CH_3), 20.68 (C_2-CH_3), 26.17 (C_l),177.54 (C_9), 141.1 ($C_{10'}$, $C_{4'}$), 137.8 ($C_{8'}$, $C_{9'}$),135.60 (C_7), 132.6 (C_5), 129.69 (C_6), 125.02 (C_3),123.2 (C_1), 120.77 (C_8), 120.47(C_4), 118.0 (C_2),63.3 (C_c, C_d), 58.1 (C_a, C_b) 54.8 (C_k), 51.4 (C_m).LCMS(m/z):- 351, 224,146(M+1)

10-(3-N-piperidinopropyl) – 2, 4-dimethylacridone (4)

One gram (0.0021 mmole) of 10-(3-N-Chloropropyl)-2, 4-dimethyl acridone was dissolved in 30ml 0f acetonitrile and 1.56g of potassium iodide and 2.6g of potassium carbonate was added and refluxed for half an hour, then it added 1.2ml of piperidine slowly. The reaction mixture was refluxed for 18 hours cooled to room temperature and extracted with chloroform. The chloroform layer was washed with water thrice, dried over anhydrous sodium sulphate and rotaevaporated. The product was purified by column chromatography to give yellow oily product which was converted into Hydrochloride salt, dried to get pure solid **(4)** obtain (yield 33%, mp 168$_oC$). $C_{23}H_{28}N_2O$.HCl, Analytical cal.: ^1H- NMRδ 7.11-8.72 (m, Ar-H, 6H), 2.40 (S, 2CH3, 6H), 2.60-2.71 (m, H_l, H_c, H_d,H_e, 8H), 3.45-4.21 (m, H_k, H_m, H_aH_b, 8H),LCMS(m/z) 349(M+) 291, 224, 211

10-(3-N-(Methylpiperazino) propyl-2, 4-dimethylacridone (5)

One gram (0.0021 mmole) of 10-(3-N-Chloropropyl)-2, 4-dimethylacridone was dissolved in 30ml of anhydrous acetonitrile and 1.13g potassium iodide and 2.18g of potassium carbonate were added and refluxed for 30 minutes. Then added 1.10g (0.34mmole, 1.22ml) of N-methylpiperazine into it slowly and refluxed for 15 hours until a substantial amount of the

product was formed as evidenced by TLC. The contents were cooled, diluted with water and extracted with chloroform. The chloroform layer was washed with water thrice, dried over anhydrous sodium sulphate and evaporated to give an oily product. The oily residue was purified by column chromatography using the solvent system chloroform: methanol (9:1) to give a light brown oil of10-[3-N-(methylpiperazino) propyl]-2, 4-dimethylacridone **(3)**. An acetone solution of the free base was treated with ethereal hydrochloride to give the hydrochloride salt that was dried over high vacuum to get pure solid **(3)** $C_{23}H_{29}N_3O.2HCl$ (yield 59%, mp 152^oC).

10-(3-[N-Diethylamino] propyl) -2, 4-dimethylacridone (6)

One gram (0.0021mmole) of 10-(3-N-Chloropropyl)-2, 4-dimethylacridone was dissolved in 60ml of anhydrous acetonitrile and 1.45g of potassium iodide and 2.42g of potassium carbonate were added and refluxed for 30 minutes. Then added slowly 1.17ml of diethylamine and refluxed for 15 hours. TLC monitored the completion of the reaction. The reaction mixture was cooled and extracted with chloroform. The chloroform layer was washed with water thrice and dried over anhydrous sodium sulphate and evaporated. The crude product was purified by column chromatography. The light brown oily product was dissolved in dry acetone and treated with ethereal hydrochloride. Hydrochloride salt of the product can be formed is 10-(3-[N-diethylamino] propyl)–2, 4-dimethylacridone **(6)**$C_{22}H_{28}N_2O.HCl$ (yield 30%, mp 137^oC).

10-(3-[N-Diethanolamino] propyl)-2, 4-dimethylacridone (7)

One gram (0.0034 mmole) of 10-(3-N-Chloropropyl)- 2, 4-dimethylacridone, 1.52g potassium iodide and 1.52g potassium carbonate in 60ml anhydrous acetonitrile were refluxed for half an hour. Then 20ml of diethanolamine was added and refluxed the content for 15 hours. The reaction mixture was cooled, extracted with chloroform. The chloroform layer was washed with water thrice and dried over anhydrous sodium sulphate and rotaevaporated. The product was purified by column chromatography $C_{22}H_{28}N_2O_3$ (yield56%, mp 193^oC).

10-(3-N-[(β-Hydroxyethyl) piperazino] propyl) –2, 4-dimethylacridone (8)

One gram (0.0021 mmole) of 10-(3-N-Chloropropyl)-2, 4-dimethylacridone was dissolved in 60ml of anhydrous acetonitrile and 1.64g of potassium iodide and 2.73g of potassium carbonate were added and refluxed for 30 minutes. Then it added slowly 1.37ml of (β-hydroxyethyl) piperazine into the flask. The mixture was refluxed for 18 hours. TLC monitored the completion of the reaction. The reaction mixture was cooled, diluted with water and extracted with chloroform. The chloroform layer was washed with water thrice and dried over anhydrous sodium sulphate and evaporated to give an oily product. The crude product was purified by column chromatography. The oily product was dissolved in dried acetone and treated with ethereal hydrochloride. Hydrochloride salt of 10-(3-N-[(β-hydroxyethyl) piperizino] propyl) – 2, 4-dimethyl acridone **(8)** was obtained $C_{24}H_{31}N_3O_2.2HCl$ (yield 52%, mp223^oC).

10-(4-N-Chlorobutyl)–2, 4-dimethylacridone (9)

One gram (0.0045 mmole) of 2, 4-dimethylacridone was dissolved in 20ml of tetrahydrofuran and added 25ml 6N Potassium hydroxide solution and 0.78g of tetrabutylammonium bromide to it. The reaction mixture was stirred at room temperature for 30 minutes. Added 1-bromo-4-chlorobutane slowly into the reaction mixture and stirred at room temperature for 24 hours. Tetrahydrofuran was evaporated and the aqueous layer was extracted with chloroform. The

chloroform layer was washed with water and organic layer is dried over anhydrous sodium sulphate and rotaevaporated. The crude product was purified by column chromatography using the solvent ratio of chloroform: methanol (9:1) to give brown crystals of 10-(4-N-chlorobutyl)-2, 4-dimethylacridone $C_{19}H_{20}NOCl$ (Yield 52%, mp134 ^{o}C).

10-(4-N-morpholinobutyl)-2, 4-dimethylacridone (10)

One gram (0.0023mmole) of 10-(4-N-Chlorobutyl)-2, 4-dimethylacridone was dissolved in 30ml of acetonitrile to which added 1.55g potassium iodide and 2.59g of potassium carbonate and refluxed for 30 minutes. Then 1.05ml of morpholine was added and refluxed for additional 24 hours. The contents were cooled and extracted with chloroform. The chloroform layer was washed with water thrice and dried. Chloroform was rotaevaporated to give an oily product. The oily product was purified by column chromatography. The light colored oily product was dissolved in dry acetone and treated with ethereal hydrochloride can be used for salting of brown oily product. So Hydrochloride salt of 10-(4-N-morpholinobutyl)-2, 4-dimethylacridone **(10)** was obtained (yield 58%, mp 148^{o}C). $C_{23}H_{28}N_2O_2$.HClAnaly.cal: $_1$H- NMRδ 7.01-8.17 (m, Ar-H, 6H), 2.1-2.4(S, 2CH_3, 6H), 2.8-2.9 (m, H_l, 4Hand H_m), 3.3-4.1(m, H_k, H_n, H_a, H_bH_c, H_d, 12H) $_{13}$C-NMRδ 17.93 (C_4-CH_3), 20.84 (C_2-CH_3), 25.01(C_l),176.94 (C_9), 140.9 (C_{10}', C_4'), 138.54 (C_8', C_9'),137.8 (C_7), 136.2 (C_5), 133.1 (C_6), 125.03 (C_3),123.3 (C_1), 120.3 (C_8), 119.9(C_4), 118.8 (C_2), 63.5(C_c, C_d), 63.3 (C_a, C_b), 56.4 (C_k), 51.3 (C_n),21.96 (C_m).LCMS(m/z): 365(M+) 351, 224, 215

10-(4-N-piperidinobutyl)-2, 4-dimethylacridone (11)

One gram (0.0023 mmole) of 10-(4-N-Chlorobutyl)-2, 4-dimethyl acridone was dissolved in 30ml 0f acetonitrile, 1.41g of potassium iodide and 2.36g of potassium carbonate were added and refluxed for half an hour, then it added 1.05ml of piperidine slowly. The reaction mixture was refluxed for 20 hours cooled to room temperature and extracted with chloroform. The chloroform layer was washed with water thrice, dried over anhydrous sodium sulphate and rotaevaporated. The product was purified by column chromatography to give light brown oily product which was converted into hydrochloride salt, dried to get pure solid of 10-(4-N-piperidinobutyl)-2, 4-dimethylacridone **(11)** (yield 52%, mp162^{o}c). : $C_{24}H_{30}N_2O$.HClAnaly.cal: $_1$H- NMRδ 7.11-8.28 (m, Ar-H, 6H), 1.75-1.73 (S, 2CH3, 6H), 2.03-2.49 (m,H_l, Hm, Hc, Hd, He, 10H), 2.49-2.80(m, H_k, H_n, H_a, H_b, 8H).LCMS(m/z) 363(M+), 224, 211, 158, 144.

10-(4-N-[Methylpiperazino] butyl) –2, 4-dimethylacridone (12)

One gram (0.0023 mmole) of 10-(4-N-Chlorobutyl)-2, 4-dimethyl acridone, 1.43g potassium iodide and 2.38g of potassium carbonate in 30ml acetonitrile were taken in a round bottom flask and refluxed for 30 minutes. Then added 1ml of N-methylpiperazine into the flask slowly and refluxed for 15 hours until a substantial amount of product was formed as evidenced by TLC. The content were cooled, diluted with water and extracted with chloroform. The chloroform layer was washed with water and dried over anhydrous sodium sulphate. Chloroform was removed by rotaevaporation to give brown oil. Oily residue was then converted into hydrochloride salt $C_{24}H_{31}N_3O$.2HCl (yield 59%, mp 183^{o}C).

10-(4-[N-Diethylamino] butyl) –2, 4-dimethylacridone (13)

One gram (0.0023 mmole) of 10-(4-N-Chlorobutyl)-2, 4-dimethylacridone was dissolved in 30ml of anhydrous acetonitrile and 1.57g of potassium iodide and 2.62g of potassium carbonate were added and refluxed for 30 minutes. Then added slowly 1.3ml of diethylamine and refluxed for 20 hours. TLC monitored the completion of the reaction. The reaction mixture was cooled and extracted with chloroform. The chloroform layer was washed with water thrice and dried over anhydrous sodium sulphate and evaporated. The crude product was purified by column chromatography and converted to hydrochloride salt by treating with ethereal hydrochloride $C_{23}H_{30}N_2O.HCl$ (yield 58%, mp 172^oC).

10-(4-[N-Diethanolamino] butyl) - 2, 4-dimethylacridone (14)

One gram (0.0023 mmole) 10-(4-N-Chlorobutyl)-2, 4-dimethylacridone was dissolved in 1.8g potassium iodide and 2.8g potassium carbonate in 30ml anhydrous acetonitrile were refluxed for half an hour. Then 1.20ml of diethanolamine was added and refluxed the content for 20 hours. The reaction mixture was cooled, extracted with chloroform, dried over anhydrous sodium sulphate and rotaevaporated. The product was purified by column chromatography $C_{23}H_{30}N_2O_3$ (yield 52%, mp 142^oC).

Table-I: Acridone Derivatives

CH3ORCH3N Comp. No.	R	Molecular Formula	Melting Point	Mol. Weight	Yield%
1	-H	$C_{14}H_{13}NO$	318 ^0C	223	68%
2	-CH_2-CH_2-CH_2-Cl	$C_{18}H_{18}NOCl$	158 ^0C	299	46%
3	**-(CH2)3-ON**	$C_{22}H_{26}N_2O_2$	159 ^0C	350	58%
4	**N-(CH2)3-**	$C_{23}H_{28}N_2O$	168 ^0C	348	33%
5	**NN-(CH2)3--3**	$C_{23}H_{29}N_3O$	152 ^0C	363	59%
6	**-(CH2)3-NCH2-CH3CH2-CH3**	$C_{22}H_{28}N_2O$	182 ^0C	373	42%
7	**-(CH2)3-NCH2-CH2-OHCH2-CH2-OH**	$C_{22}H_{28}N_2O_3$	193 ^0C	368	56%
8	**-(CH2)3-CH2-CH2-OHNN**	$C_{24}H_{31}N_3O_2$	223 ^0C	393	52%
9	-CH_2-CH_2-CH_2-CH_2-Cl	$C_{19}H_{20}NOCl$	134 ^0C	314	52%
10	**-(CH2)4-ON**	$C_{23}H_{28}N_2O_2$	148 ^0C	364	58%
11	**N-(CH2)4-**	$C_{24}H_{30}N_2O$	162 ^0C	362	53%
12	**NN-CH3-(CH2)4-**	$C_{24}H_{31}N_3O$	183 ^0C	377	59%
13	**-(CH2)4-NCH2-CH3CH2-CH3**	$C_{23}H_{30}N_2O$	172 ^0C	387	58%
14	**-(CH2)4-NCH2-CH2-OHCH2-CH2-OH**	$C_{23}H_{30}N_2O_3$	142 ^0C	382	52%
15	**CH2-CH2-OHNN-(CH2)4-**	$C_{25}H_{33}N_3O_2$	181 ^0C	407	56%

C H

10-(4-N-[(β-Hydroxyethyl) piperizino] butyl) –2, 4-dimethylacridone (15)

One gram (0.0033 mmole) of 10-(4-N-Chlorobutyl)-2, 4-dimethylacridone was dissolved in 30ml of anhydrous acetonitrile and 1.57g of potassium iodide and 2.62g of potassium carbonate were added and refluxed for 30 minutes, then it added slowly 2.1ml of β-hydroxyethyl piperazine into the flask. The mixture was refluxed for 20 hours. TLC monitored the completion of the reaction. The reaction mixture was cooled, extracted with chloroform. The chloroform layer was washed with water thrice and dried over anhydrous sodium sulphate and evaporated. The crude product was purified by column chromatography and converted to hydrochloride salt by treating the residue with ethereal hydrochloride$C_{25}H_{33}N_3O_2.2HCl$ (yield 52%, mp 142^0C).

Anticancer activity:

Assay of Cytotoxicity and Reversal of MDR

MCF-7 and MCF-7/ADR cells were placed into 96-well tissue culture plates at approximately 15% confluency and were allowed to attach and recover for 24 hours. The cells were then treated with varying concentrations (as allowed by solubility) of the test compound in the presence of 0 to 50nM vinblastine for 48 hours according to previously described procedures. After 48 hours, cell survival was assayed using the Sulforhodamine B (SRB) binding assay. The percentage of cells killed was calculated as the percentage decrease in SRB binding as compared with control cultures and was taken from the mean of the absorbance measurements of three equally treated wells. Reversal of MDR is indicated if the compound enhanced the toxicity of vinblastine toward the NCI/ADR cells[6-12]. The reversal index (P-gp antagonism score) was calculated as the percentage of surviving NCI/ADR cells in the absence of vinblastine/the percentage of surviving NCI/ADR cells in the presence of vinblastine. Control cultures included equivalent amounts of ethanol (as the solvent control), which does not modulate the growth or drug sensitivity of these cells at the doses used in these studies. Inhibition of P-gp was manifested as the ability of the compound to potentiate the cytotoxicity of vinblastine toward the NCI/ADR cells. To assess the toxicity of the compounds toward drug sensitive cells, the effects of the test modulators on the growth of drug-sensitive MCF-7 cells were determined by the same methods. To test for reversal of MDR, MCF-7/ADR cells were placed into 96-well tissue culture plates at approximately 15% confluence and were allowed to attached and recover for 24 hour. The cells were then treated with varying concentrations (as allowed by solubility) of the test compound in the presence of 0 or 1nM vincristine for 48 hours as above. After 48 hour, cell survival was assayed using the SRP binding assay. Reversal of MDR is indicated if the compound enhanced the toxicity of vincristine toward the MCF-7/ADR cells. The reversal index (MRP1 antagonism score) was calculated as the percentage of surviving MCF-7/ADR cells in the absence of vincristine/the percentage of surviving MCF-7/ADR cells in the presence of vincristine. Control cultures included equivalent amounts of ethanol (as the solvent control), which does not modulate the growth or drug sensitivity of these cells at the doses used in these studies[13-17].

RESULTS AND DISSCUSSION

From the synthesized fifteen acridone derivatives all compounds were screened for anti-cancer and anti-MDR activity using verapamil as a control against breast cancer MCF-7 cells and their drug resistant strain MCF-7/ADR cells[18-20]. The data in the **Table IV** and **V** indicate that the compound **10, 13, 14** & **15** and demonstrated the greatest effect followed by compound **10 >13**

>14 > 15 > 11 > 8 > 12 > 7 >6 > 4 > 5 >3 > & 1. Only four acridone derivatives **(10, 13, 14** & **15)** like verapamil were able to completely reverse the 25-fold resistance of MCF-7/ADR cells to vinblastine. From the anticancer and anti-MDR screening it was found that the compounds showed significant activity at the given concentration levels. Hence these compounds appear to be promising anticancer and anti-MDR agents, perhaps the tricyclic N^{10} -substituted acridone with a dimethyl group at position C-2 and C-4 and a secondary amine side chain containing a tertiary amino group at a distance of at least three to four carbon atoms from the tricyclic ring is responsible for marked anti-MDR activity.

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